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Does waiting for surgery matter? How time from diagnostic MRI to resection affects outcomes in newly diagnosed glioblastoma

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Abstract

OBJECTIVE—Maximal safe resection is the standard of care for patients presenting with lesions concerning for glioblastoma (GBM) on magnetic resonance imaging (MRI). Currently, there is no consensus on surgical urgency for patients with an excellent performance status, which complicates patient counseling and may increase patient anxiety. This study aims to assess the impact of time to surgery (TTS) on clinical and survival outcomes in patients with GBM.

METHODS—This is a retrospective study of 145 consecutive patients with newly diagnosed IDH–wild-type GBM who underwent initial resection at the University of California, San Francisco, between 2014 and 2016. Patients were grouped according to the time from diagnostic MRI to surgery (i.e., TTS): ≤ 7, > 7–21, and > 21 days. Contrast-enhancing tumor volumes (CETVs) were measured using software. Initial CETV (CETV1) and preoperative CETV (CETV2) were used to evaluate tumor growth represented as percent change (ΔCETV) and specific growth rate (SPGR; % growth/day). Overall survival (OS) and progression-free survival (PFS) were measured from the date of resection and were analyzed using the Kaplan-Meier method and Cox regression analyses.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Tables and Figures. https://thejns.org/doi/suppl/10.3171/2023.5.JNS23388.

RESULTS—Of the 145 patients (median TTS 10 days), 56 (39%), 53 (37%), and 36 (25%) underwent surgery ≤ 7, > 7–21, and > 21 days from initial imaging, respectively. Median OS and PFS among the study cohort were 15.5 and 10.3 months, respectively, and did not differ among the TTS groups (p = 0.81 and 0.17, respectively). Median CETV1 was 35.9, 15.7, and 10.2 cm^3 across the TTS groups, respectively (p < 0.001). Preoperative biopsy and presenting to an outside hospital emergency department were associated with an average 12.79-day increase and 9.09-day decrease in TTS, respectively. Distance from the treating facility (median 57.19 miles) did not affect TTS. In the growth cohort, TTS was associated with an average 2.21% increase in ΔCETV per day; however, there was no effect of TTS on SPGR, Karnofsky Performance Status (KPS), postoperative deficits, survival, discharge location, or hospital length of stay. Subgroup analyses did not identify any high-risk groups for which a shorter TTS may be beneficial.

CONCLUSIONS—An increased TTS for patients with imaging concerning for GBM did not impact clinical outcomes, and while there was a significant association with ΔCETV, SPGR remained unaffected. However, SPGR was associated with a worse preoperative KPS, which highlights the importance of tumor growth speed over TTS. Therefore, while it is ill advised to wait an unnecessarily long time after initial imaging studies, these patients do not require urgent/emergency surgery and can seek tertiary care opinions and/or arrange for additional preoperative support/resources. Future studies are needed to explore subgroups for whom TTS may impact clinical outcomes.

Keywords

glioblastoma; wait time; tumor growth; outcomes; time to surgery

Glioblastoma (GBM) is the most common primary malignant brain tumor, and despite recent therapeutic advancements, the 5-year survival rate remains unchanged even with maximal resection and adjuvant chemoradiation.[1,2] Well-known prognostic factors include patient age, Karnofsky Performance Status (KPS), postoperative extent of resection (EOR), amount of residual tumor volume on postoperative imaging, and tumor molecular genotype.[3,4]

While the upfront therapeutic management of GBM is well established, the timing for delivery of this standard of care is unclear. Although recent studies have attempted to evaluate survival and the functional implications of adjuvant chemoradiation timing,[5–8] less is known regarding the effects of time to definitive resection after initial magnetic resonance imaging (MRI) demonstrates features concerning for high-grade glioma. One study has found that for GBM patients presenting only with seizures, a decreased time to surgery (TTS) and lack of tumor growth during the interval waiting period were associated with a survival benefit.[9] Alternatively, it has been shown that waiting for up to 30 days was not associated with worse outcomes.[10] Moreover, the factors, such as medical comorbidities, patient location, and insurance status, that may influence TTS remain poorly elucidated.

While an increased TTS can contribute to patient anxiety, a lack of consensus on how to counsel patients can make it difficult to provide firm recommendations with respect to operative scheduling. Certainly, in instances of a declining performance status, progressive symptoms, or evidence of significant mass effect and herniation syndromes, surgical

intervention becomes more urgent. To address this knowledge gap, we retrospectively reviewed newly diagnosed GBM patients who had undergone resection to elucidate factors that impact TTS and clarify its prognostic value.

Methods

Patient Selection

This is a retrospective cohort study of patients with newly diagnosed IDH–wild-type GBM who underwent initial resection at the University of California, San Francisco (UCSF) between January 1, 2014, and December 30, 2016. Adult patients (age ≥ 18 years) were included if they had pathological confirmation of the diagnosis and pre- and postoperative MRI available to determine EOR. Exclusion criteria were as follows: chemotherapy or radiation treatment prior to definitive resection, a history of confirmed low-grade glioma that progressed to GBM, or limited follow-up after a pathological GBM diagnosis. Of the 155 patients initially reviewed, immunohistochemistry was used to detect the presence of an IDH mutation in 145 (93.5%) cases, whereas next-generation sequencing was performed in 10 (6.5%) cases. The final cohort included 145 patients after excluding 5 IDH-mutated tumors (which are no longer considered GBM according to the 2021 World Health Organization diagnostic criteria), 2 previously treated patients, 2 patients without follow-up after their initial diagnosis, and 1 transfer because of intraoperative complications during an attempted resection.

Of the 129 patients with two separate preoperative MRI studies available for volumetric measurement, those with a difference between their initial contrast-enhancing tumor volume (CETV1) and preoperative CETV (CETV2) of more than 0.00 cm^3 were included in the growth cohort (n = 77). Tumor growth analyses were carried forward in this group, while the remaining 52 patients displayed no or negative growth between CETV1 and CETV2.

The Institutional Committee on Human Research at UCSF reviewed and approved this study. Since this study is a retrospective analysis of information found in the medical record, informed consent to publication was not required, although written informed consent was obtained at the time of treatment.

Recorded Variables

Electronic medical records (EMRs) were retrospectively reviewed for demographic and clinical data. Tumor location was based on the neuroradiologist report on the preoperative MRI scan. The use of adjuvant therapies including radiation and temozolomide as well as participation in clinical trials was recorded when available. Distance from the hospital was calculated as the driving distance from the patient's home zip code to the treating facility. If driving distance was not applicable (e.g., international), then the Euclidian distance was used. Crosswalk data from the Dartmouth Atlas Project[11] and shapefiles obtained from the Centers for Medicare & Medicaid Services[12] were used to generate the treating facility's health service area (HSA) boundaries. Geocoded patient zip codes were then geographically plotted with respect to the HSA boundary to classify patients as inside or outside the primary service area.

Imaging and Volumetric Analysis

Initial, preoperative, and postoperative T1-weighted MRI studies with and without gadolinium enhancement were obtained for each participant along with the sequence protocol, slice count, and slice thickness. Brainlab Smartbrush software was used to measure tumor volume. CETV was determined as the region within the lesional contrast enhancement on T1-weighted post–gadolinium contrast sequences. A region of interest was drawn around the tumor in three planes for each slice in the sequence, and the volume was calculated from the circumscribed region. In addition, we measured the maximum two-dimensional diameter (2DD) in the axial plane. For both CETV and 2DD, we calculated the absolute difference and the percent change (ΔCETV and Δ2DD) from initial (CETV1 and 2DD1) to preoperative (CETV2 and 2DD2) MRI. EOR was calculated in the standard fashion using the postoperative CETV (CETV3) and CETV2 as follows: EOR = [(CETV2 − CETV3)/CETV2] × 100. Specific growth rate (SPGR) was used to quantify the change in volume per day where TTM was the number of days between initial and preoperative MRI studies and was calculated using the following equation (expressed as % growth/day): SPGR = [ln(CETV2/CETV1)/TTM] × 100.

Statistical Analysis

All statistical analyses were performed using R statistical software (version 4.2.1, R Foundation for Statistical Computing). Categorical data are presented as count and frequency, whereas Shapiro-Wilk tests were used to assess continuous variables for normality. The mean ± standard deviation and median (interquartile range) were used to present parametric and nonparametric data, respectively. One-way ANOVA was used to compare continuous data among the 3 TTS groups, whereas Fisher's exact test was used for categorical data. Nonparametric equivalents were used as appropriate. CETV1, 2DD1, CETV2 were categorized using the R package CatPredi,[13] which optimizes the area under the curve for the discriminative value within logistic and Cox proportional hazard regression models.

Univariate and multivariate logistic and linear regression analyses were used to evaluate predictors of outcomes represented as odds ratios and β coefficients, respectively. Variables with a p value < 0.2 on univariate analyses were included in the final multivariate model. Overall survival (OS) and progression-free (PFS) survival were measured from the date of resection. EMR notes by the treating neuro-oncologist were used to determine progression, which was defined as imaging changes or symptoms concerning for disease progression that led to either a change in therapy or transition to comfort care. OS and PFS were analyzed with Kaplan-Meier and log-rank tests for comparison between groups, while Cox regression analysis was used for prognostication within predefined subgroups. In addition, a generalized boosted model (R package twang[14]) was used to estimate the propensity scores for each TTS group while using age and CETV1 as covariates. Thereafter, the propensity scores were used in a weighted Cox regression analysis to evaluate the effect of TTS on OS while accounting for these baseline differences.

For survival analysis, we calculated power based on a noninferiority design with the hypothesis that a longer TTS was not inferior to a shorter TTS. Preliminary power analyses

were performed using groups determined by the TTS median of 10 days as a cutoff, where TTS was ≤ 10 days in group 1 and > 10 days in group 2. Given the hazard rates of 0.077 (median OS 9 months) and 0.062 (median OS 11.1) in groups 1 and 2, respectively, we would achieve 83.3% power at a 0.05% significance level assuming an HR of 0.805 and a noninferiority margin of 1.25 with 36 months of accrual and 72 months of total follow-up time.

Results

Patient Characteristics

Of the 145 patients in the final cohort (58 [40%] females, median age 62.4 years, median TTS 10 days), 56 (39%), 53 (37%), and 36 (25%) underwent surgery ≤ 7, > 7–21, and > 21 days after initial imaging diagnosis, respectively. The median TTS in each group was 4, 11, and 30 days, respectively. There was a maximum wait time of 82 days in the longest TTS group. The median distance from the treating hospital was 57.19 (range 0–2575.49) miles, and 10 (6.9%) patients were within the HSA, with neither factor differing among the groups. Medicare was more common in patients undergoing surgery later (i.e., > 7–21 days), whereas Medicaid was the predominant provider in the other groups ($p = 0.04$ and 0.02, respectively). Table 1 details characteristics of the study population.

Initial Presentation and TTS

At initial presentation to the outside hospital (OSH), a biopsy was performed in 24 (17%) patients before they underwent definitive resection at our facility, and this occurred more frequently among those with the longest wait time (i.e., > 21 days; $p < 0.001$). Of the 104 (74%) physician-initiated transfers or referrals to the treating hospital, 52 (50%) were for escalation of care as inpatients, 31 (30%) were referrals from primary care providers or neurologists, and 21 (20%) were for motor or language mapping. Patient-initiated second opinions occurred more frequently in the > 7–21 and > 21 days groups (13 [25%] and 10 [28%], respectively) compared to the ≤ 7 days group (8 [14%]; $p < 0.001$). Presentation location to the treating facility and tumor laterality also differed significantly among the TTS groups (Table 1). Patients having surgery within 7 days more frequently presented to the emergency department (ED) at an OSH and were more often admitted as direct transfers to the treating facility ($p < 0.001$). Interestingly, left-sided tumors were more frequent in the > 7–21 and > 21 days groups ($p = 0.031$). The median preoperative KPS was 80 and equal among the TTS groups.

On univariate analysis, statistically significant ($p < 0.05$) predictors of a longer TTS included prior biopsy at an OSH, Medicare insurance, transfer for mapping, referral from another physician, delay/transfer for a second opinion, increased distance from the treating facility, and preoperative seizures as the presenting symptom. Statistically significant ($p < 0.05$) predictors of a shorter TTS included presentation to an OSH ED, preoperative behavioral changes, preoperative nausea/vomiting, increased CETV1, and increased 2DD1. On multivariate analysis, while controlling for the variables included in the final model (Supplementary Table 3), preoperative biopsy was associated with an average increase of 12.79 days in the TTS (95% CI 5.13–20.44, $p = 0.001$) and presenting to the OSH ED was

associated with an average decrease of 9.09 days in the TTS (95% CI −15.65 to −2.54, p = 0.007).

Tumor Volume and Growth

Details of the MRI characteristics and volume measurements for the entire cohort are listed in Supplementary Table 1. Overall, EOR was no different among the TTS groups, that is, ≤ 7 days (98.2), > 7–21 days (98.4), and > 21 days (97.8; p > 0.8). Likewise, CETV3 was no different among TTS groups, with an overall median residual volume of 0.49 cm^3.

In the growth cohort, the median CETV1 was 30.96, 14.40, and 6.03 cm in the TTS groups (i.e., ≤ 7, > 7–21, and > 21 days, respectively; p < 0.001; Supplementary Table 2). Figure 1A shows that the > 21 days group had a significantly smaller CETV1 than both the > 7–21 days and ≤ 7 days groups. The median 2DD1 was significantly larger in the ≤ 7 days group as compared to the > 21 days group (p = 0.02; Fig. 1C). On average, CETV2 was significantly larger than CETV1 in all TTS groups (Fig. 2A).

Median ΔCETV was greater in the > 21 days group (126.86%) than in the > 7–21 days (24.10%; p < 0.001) and ≤ 7 days (11.02%; p < 0.001) groups (Fig. 2B). Likewise, median Δ2DD was larger in those undergoing surgery later and was significantly different among all 3 groups on pairwise comparisons (Fig. 2C). However, SPGR and EOR did not differ among the groups (Fig. 2D and E).

While controlling for CETV1 and 2DD1 in a multivariate analysis, a 1-day increase in TTS was significantly associated with an average 2.21% increase in ΔCETV (95% CI 0.37%–4.05%, p = 0.02) and 0.65% increase in 2DD (95% CI 0.15–1.15, p = 0.012). However, there was no significant association between TTS and SPGR (β −0.13, 95% CI −0.27 to 0.02, p = 0.08) (Supplementary Table 4). Interestingly, when examining the effect of SPGR on EOR, EOR was resilient to changes in SPGR in the entire cohort (Fig. 3A) and the growth cohort (Fig. 3B), despite differences in TTS and CETV1.

Clinical Outcomes

In the entire cohort, multivariate analyses demonstrated that TTS did not significantly impact disposition location, length of stay, postoperative complications, or any other outcome-related variable (Supplementary Table 5).

In the cohort of patients that demonstrated tumor growth between the initial and preoperative scans (growth cohort), neither TTS, SPGR, nor ΔCETV was associated with early or late complications, new postoperative deficits, improvements in pre- or postoperative deficits, home discharge, or hospital length of stay (Supplementary Table 4). However, an increased SPGR was associated with a lower preoperative KPS (β −0.84, 95% CI −1.46 to −0.22, p = 0.009). Interestingly, multivariate analyses revealed that an increased EOR was associated with improvements in preoperative deficits. Otherwise, in this cohort, biopsy prior to resection was associated with a decreased pre- and postoperative KPS (β −10.62, 95% CI −17.83 to −3.41, p = 0.005; and β −7.27, 95% CI −14.35 to −0.19, p = 0.04, respectively) and no improvement in preoperative deficits (OR 0.20, 95% CI 0.05–0.87, p = 0.03).

Survival Outcomes

The median OS in the entire cohort was 15.5 months and did not differ among the TTS groups (Fig. 4A; p = 0.81). Likewise, median PFS in the entire cohort was 10.3 months and did not differ among the groups (Fig. 5A; p = 0.17). OS was equal between those without and those with a biopsy prior to definitive treatment, with a positive absolute change in CETV, and this remained true even in the patients with a ≥ 20% change in CETV (Fig. 6). Moreover, being within the treating facility's HSA did not prolong OS (13.7 vs 16.6 months, p = 0.6) or PFS (9.0 vs 10.4 months, p = 0.8). Additional subgroup analyses did not reveal any survival advantage in having a shorter TTS (Supplementary Fig. 1). Cox regression analyses did not reveal any association between TTS and survival within subgroups (Fig. 7). Finally, after balancing the cohorts on CETV1 and age with propensity matching, OS remained unaffected by TTS on weighted Cox regression analysis (Supplementary Table 6).

TTS Outliers

TTS outliers (TTS > 46.88 days) included 10 patients (50% female, median age 60.5 years, median TTS 57.5 days) with a median distance of 204.72 miles from the treating facility, private insurance in 60%, and Medicare coverage in 40%. Delays were primarily attributable to outside provider scheduling delays, outside provider diagnostic errors, and medical comorbidities (Supplementary Table 7). Despite differences in CETV1, CETV2, ΔCETV, and SPGR, EOR was ultimately unaffected in patients with an abnormally long TTS (Supplementary Fig. 2). In addition, TTS in these patients did not appear to affect postsurgery survival time, and neither did EOR, ΔCETV, or SPGR modify this relationship (Supplementary Fig. 3). Finally, it is important to note that without these outliers, the maximum TTS decreased from 82 to 41 days.

Discussion

TTS in patients diagnosed with GBM is a potential source of concern for patients, providers, and the healthcare system. Currently, wait times to GBM resection vary greatly between patients and institutions, and there is no consensus on how to counsel patients on surgical urgency. This study is one of the few to evaluate the impact of TTS on patients with a new GBM diagnosis and, to our knowledge, is the only study to consider distance from the treating facility and the reason for delay or transfer. Overall, we report a median TTS of 10 days, which is lower than data reported elsewhere.[10,15] In addition, our results demonstrated that a longer TTS is not necessarily detrimental to patients in this cohort.

In our study, on multivariate analyses, undergoing a biopsy before definitive resection was associated with a significantly longer TTS, whereas presenting to an outside ED before definitive resection was associated with a significantly shorter TTS. Moreover, patients who waited longer to undergo resection experienced a greater ΔCETV but not SPGR, which may be a more accurate representation of tumor growth and tumor aggressiveness.[16] Importantly, ΔCETV, SPGR, and TTS were not associated with OS on multivariate analyses. Additionally, ΔCETV and TTS were not associated with postoperative KPS, postoperative deficits, or preoperative deficit status following surgery. However, a greater SPGR was associated with a lower preoperative KPS, which suggests that faster-growing tumors are

more likely to cause greater functional impairment regardless of TTS. In the growth cohort, biopsy prior to resection was significantly associated with a decreased pre- and postoperative KPS and a lack of improvement in preoperative deficits. Taken together, while current data are somewhat limited by sample size, biopsies prior to resection for lesions in which the differential diagnosis is reasonably certain to be limited to GBM may unnecessarily prolong treatment, add costs, and/or potentially complicate incision planning during definitive resection without offering benefit to the patient; however, additional studies are needed to support these associations. Regarding tumor growth, there is limited high-quality research on the effect of preoperative change or growth in CETV on survival. One study has demonstrated that, only after 12 months, a slower pretreatment tumor growth rate was associated with a survival benefit,[17] a finding that is likely limited by lead-time bias considering the median survival time of the disease. Meanwhile, a pre–Stupp era study that measured tumor-doubling volume without modern segmentation techniques in a small mixed-pathology cohort argued that tumor growth was directly associated with survival.[18] In our unique, direct analysis of ΔCETV, SPGR, and Δ2DD, we failed to identify a significant association with survival, and in combination with the lack of an association with EOR, we posit that interim volumetric growth on MRI has no effect on survival.

TTS has been more extensively studied in other oncological surgical subspecialties. A study of TTS in 408 patients with colorectal cancer and pursuing resection demonstrated no difference in oncological outcomes among patients who waited less than 4, 4–8, and more than 8 weeks.[19] In this field, factors such as American Society of Anesthesiologists physical status, body mass index, and tumor location (right colon vs left colon vs rectal) were found to have an effect on TTS as opposed to oncological factors such as tumor-node-metastasis (TNM) staging.[19] Conversely, in a large study evaluating TTS for breast cancer patients, the authors demonstrated that each 30-day decrease in TTS conferred a benefit comparable to some standard therapies.[20] Similarly, in a large study of patients with lung cancer, delayed resection, defined as 8 weeks or longer, was associated with a decreased median survival and a greater likelihood of pathological upstaging.[21] In a study of 265 veterans with lung cancer, those with larger lung nodules were taken to surgery earlier,[22] similar to our findings.

In the few studies that have evaluated TTS in gliomas, results have been mixed.[9,10,15,23] Flanigan et al. found that presenting to the ED and increased peritumoral edema on MRI were associated with a shorter TTS.[9] In their study, the authors also argue that in patients presenting only with seizures, a shorter TTS may offer a survival benefit.[18,19] Interestingly, initial presentation to the ED for a GBM has been associated with worse OS.[23,24] Yet in our study, many patients in the ≤ 7 days group presented to an OSH ED and were transferred for surgery, which did not affect survival compared to patients with slightly longer wait times. More similar to our findings, Müller et al. demonstrated in 1033 GBM patients (median TTS 13 days) that TTS was not associated with survival, and De Swart et al. reported a similar relationship in 4589 GBM patients (median TTS 18 days).[10,15] We also found no difference in pre- or postoperative KPS among the TTS groups unlike the association reported by De Swart et al. Likewise, our analyses also revealed that TTS did not affect EOR or residual tumor volume and that EOR was unaffected by differences in CETV2. Moreover, in our cohort, those undergoing surgery earlier had larger initial tumor volumes, and while this variable has historically demonstrated a nonsignificant relationship

with survival,[25] we sought to evaluate whether TTS was important in certain tumor volume subgroups. Ultimately, median OS did not differ among TTS categories when grouped by CETV1 ≥ 17 or < 17 cm^3. Uniquely, we also evaluated distance from the treating facility, delay/transfer reason, and whether the delay or transfer was initiated by the patient or physician. In these analyses, distance from the treating facility and delay/transfer initiator were equivocal among the groups. However, patients undergoing surgery sooner were more likely to require a higher level of care, whereas second opinions and referrals were more common in the longer TTS groups.

The surgical urgency of GBM resection is multifaceted and nuanced; however, there are some benefits to scheduling surgery in a semi-acute but nonurgent/nonemergency fashion. For example, high-volume centers are more likely to provide treatment rather than no treatment at all.[26] In addition, there is extensive literature supporting a survival benefit associated with obtaining treatment at high-volume academic centers,[26–30] even when patients are required to travel long distances for care.[31] In conjunction with a recent meta-analysis supporting these findings,[32] it would be particularly difficult to suggest that hastening treatment is beneficial to the patient, unless absolutely necessary. A semi-acute time frame allows neurosurgeons to obtain necessary preoperative functional assessments and assemble the proper team including a dedicated neuro-anesthesiologist, which alone has been associated with superior outcomes with regard to neurological complications and length of stay.[33] In combination with a dedicated brain tumor neurosurgeon, the pair is associated with an improved EOR as well.[33] In fact, as compared to an emergency-based, consultant-centric practice, an organized, multidisciplinary elective-based system not only improves access to standard, best-practice GBM therapy, but also reduces cost of care and length of stay and produces survival times similar to those of a clinical trial.[34] Thus, providers can make an educated assessment of the risks and benefits of presurgical medical optimization, more accurately educate their patients, and encourage them to seek additional opinions. All the while, these results suggest that phase 0 clinical trials, which may generate useful pharmacokinetic/pharmacodynamic data, can be offered to patients with little to no harm. Patients can arrange for additional support and resources at home and better prepare their personal and professional responsibilities for an upcoming leave of absence. Given the findings of this study, patients found to have an MRI lesion concerning for GBM should be scheduled for definitive resection in a semi-urgent manner.

While these findings support the notion that patients can tolerate modest wait times before resection, we are certain that there is a point beyond 21 days when there is an inflection in clinical outcomes and that exceptionally long wait times would be ill-advised. Additionally, it is important to note that patients with terminal illnesses such as GBM are likely to face anxiety and an impaired quality of life (QOL) while waiting for their procedure.[35–37] Thus, it is important to balance the impact on oncological outcomes with patient comfort and anxiety. Therefore, the results of this study can be used when counseling patients on the impact of TTS, particularly in resource-limited settings. In the future, survey metrics can be used to determine if anxiety measures and QOL metrics are different between patients in the early and late TTS groups.

This study is primarily limited by its retrospective evaluation of the effect of TTS on outcomes, both of which are likely affected by unidentified confounding variables. Thus, this cohort is potentially missing patients who developed unresectable lesions, patients who were too unstable for transfer, and patients in resource-limited settings, which limits the generalizability of our findings. Similarly, information on QOL, neurological symptoms, KPS, and corticosteroid requirements during the waiting period was unavailable and may have worsened while waiting. Likewise, the time from initial symptom onset to imaging diagnosis was unavailable given the patient presentations to an OSH, and as a result any delays associated with nonspecific or subtle symptoms are unaccounted for. The study population was limited to patients with pathologically confirmed diagnoses, so unless a biopsy is performed, this diagnostic certainty is typically unavailable when scheduling surgery. While the study's power is limited in detecting subtle differences in survival, we believe we mitigated this with our noninferiority design supporting our reasonably certain conclusion that an increased TTS is not inferior to a shorter TTS. Likewise, the relatively small growth cohort may have limited analytical power involving these patients. Furthermore, pre- and postoperative imaging was consistently performed at a single institution using the same protocol, in contrast to the sequence type, slice count, and slice thickness of initial MRI, often performed at an OSH, which may have influenced volumetric analyses. Future studies should evaluate radiographic factors associated with rapid tumor growth (e.g., appearance on diffusion or perfusion sequences), which may impact surgical urgency given the risk of growth into functional regions. Finally, we solely distinguished TTS ≤ 7, > 7–21, and > 21 days; therefore, these data do not directly evaluate TTS > 21 days. Although our TTS outlier analyses included only 10 patients, there appeared to be little to no effect after 21 days; therefore, we ultimately included them in the final cohort. Nonetheless, future work is needed to determine if there is a critical period during which surgery is more beneficial for survival and postoperative outcomes.

Conclusions

Patients with larger GBMs were taken to surgery sooner; however, a longer TTS did not impact OS, PFS, or pre- and postoperative KPS, despite interim tumor growth. These findings can help to counsel GBM patients on the best treatment options, enable surgeons to provide an educated risk assessment of presurgical medical optimization, and encourage a semi-urgent timeline to surgery for optimal patient comfort. Future studies are warranted to define the optimal window for surgical intervention based on patient and lesion characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

2DD	two-dimensional diameter
2DD1	initial 2DD

2DD2	preoperative 2DD
Δ2DD	percent change from 2DD1 to 2DD2
ΔCETV	percent change from CETV1 to CETV2
CETV1	initial contrast-enhancing tumor volume
CETV2	preoperative CETV
CETV3	postoperative CETV
ED	emergency department
EMR	electronic medical record
EOR	extent of resection
GBM	glioblastoma
HSA	health service area
KPS	Karnofsky Performance Status
MRI	magnetic resonance imaging
OS	overall survival
OSH	outside hospital
PFS	progression-free survival
QOL	quality of life
SPGR	specific growth rate
TTS	time to surgery
UCSF	University of California, San Francisco

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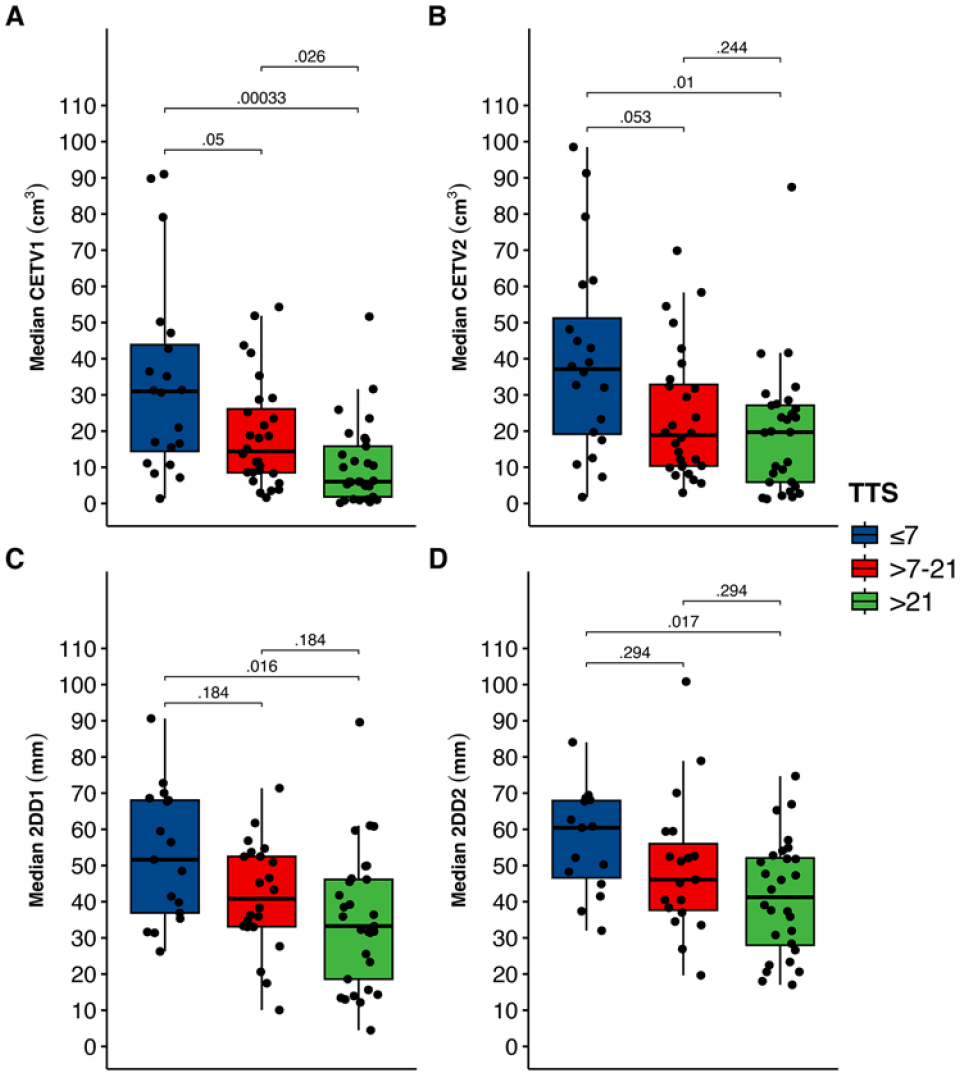

FIG. 1.

TTS category comparisons in CETV1 (**A**), CETV2 (**B**), 2DD1 (**C**), and 2DD2 (**D**) in the growth cohort (n = 77). Figure is available in color online only.

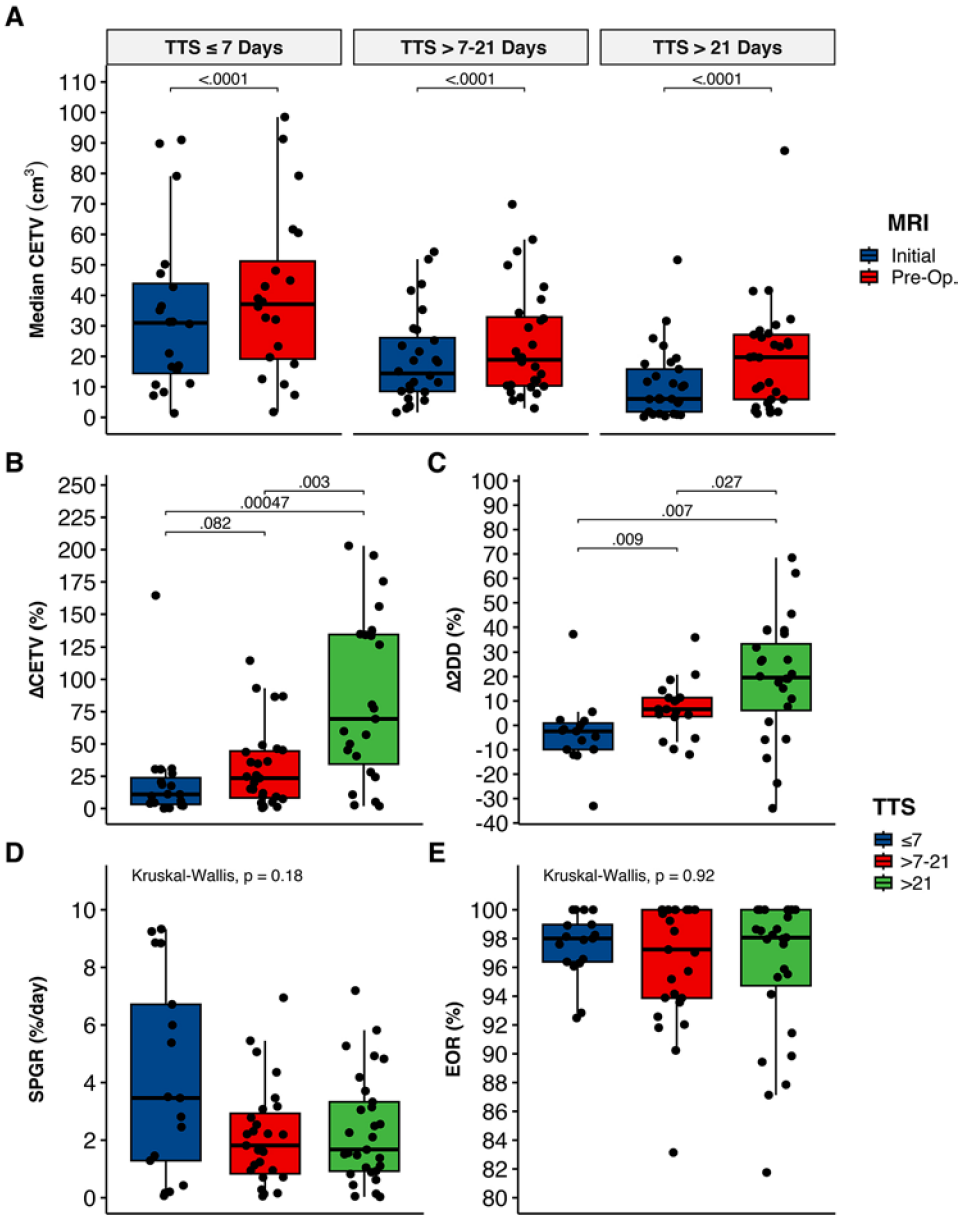

FIG. 2.

Volumetric analyses in the growth cohort (n = 77) including within-group and between-group TTS category comparisons. **A:** Within each TTS category, CETV2 significantly differed from CETV1. **B:** ΔCETV was significantly larger in the > 21 days group versus the > 7–21 days and ≤ 7 days groups. **C:** Δ2DD was significantly different among all groups and increased with a greater TTS. **D:** SPGR did not differ among the groups. **E:** EOR did not differ among the groups. Pairwise comparisons were performed only if the Kruskal-Wallis test was significant ($p < 0.05$). Outliers based on each variable were removed in comparisons featured in panels B–E for improved visualization and pairwise comparisons. Figure is available in color online only.

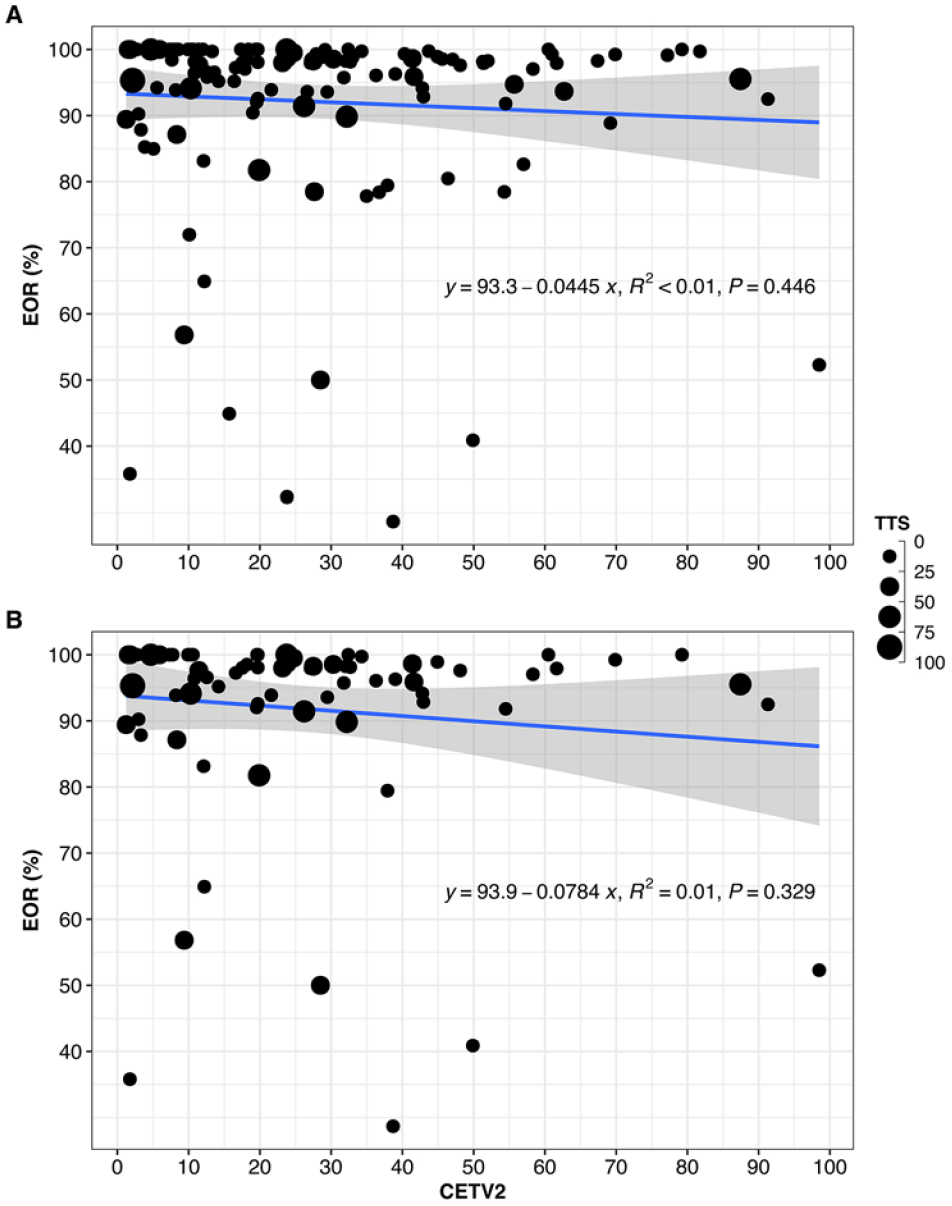

FIG. 3.

EOR analyses as a function of CETV2 and TTS (size of *black dots*). CETV2 did not affect EOR in the entire cohort (**A**) or the growth cohort (**B**). TTS did not appear to modify this relationship. Figure is available in color online only.

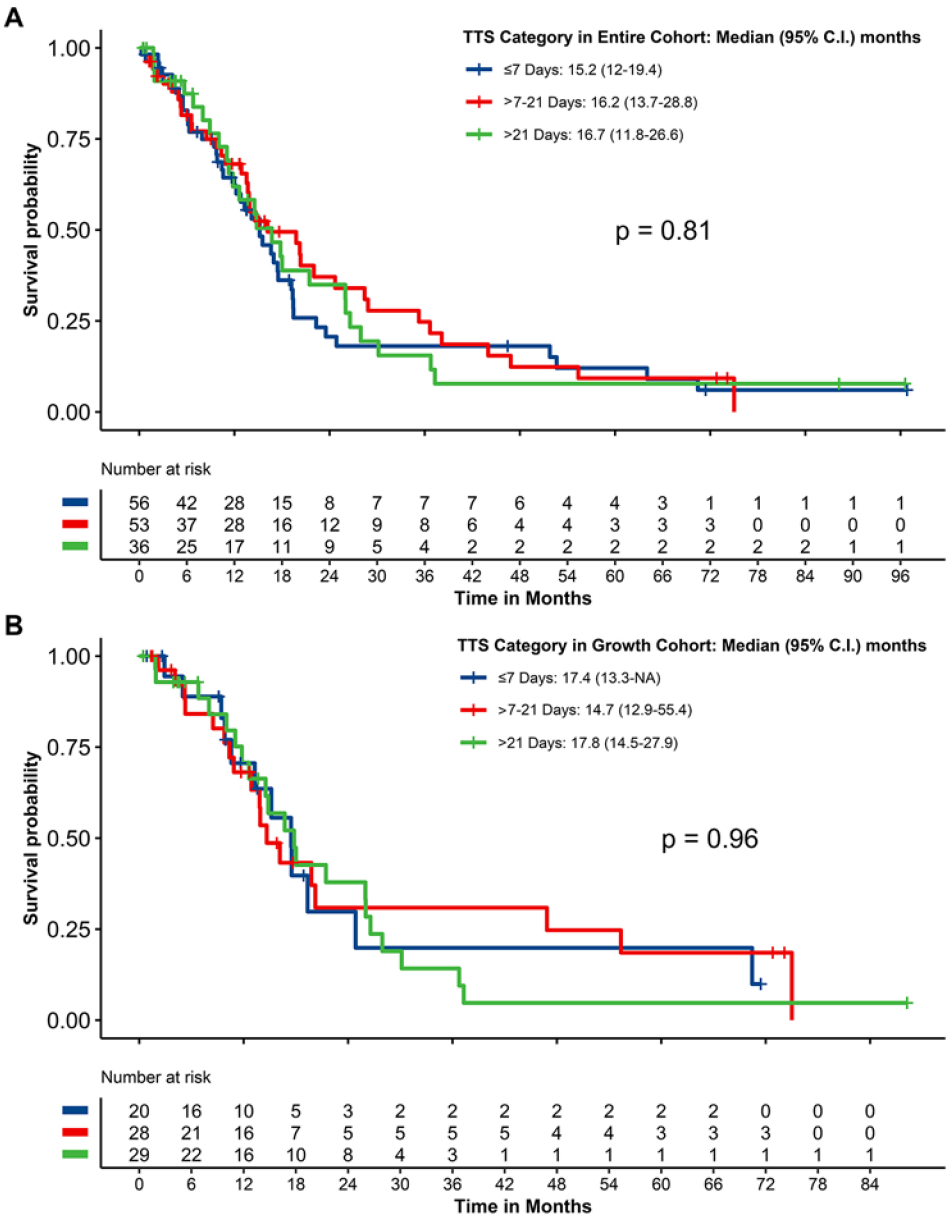

FIG. 4.

OS by TTS category in the entire cohort (**A**) and growth cohort (**B**). Figure is available in color online only.

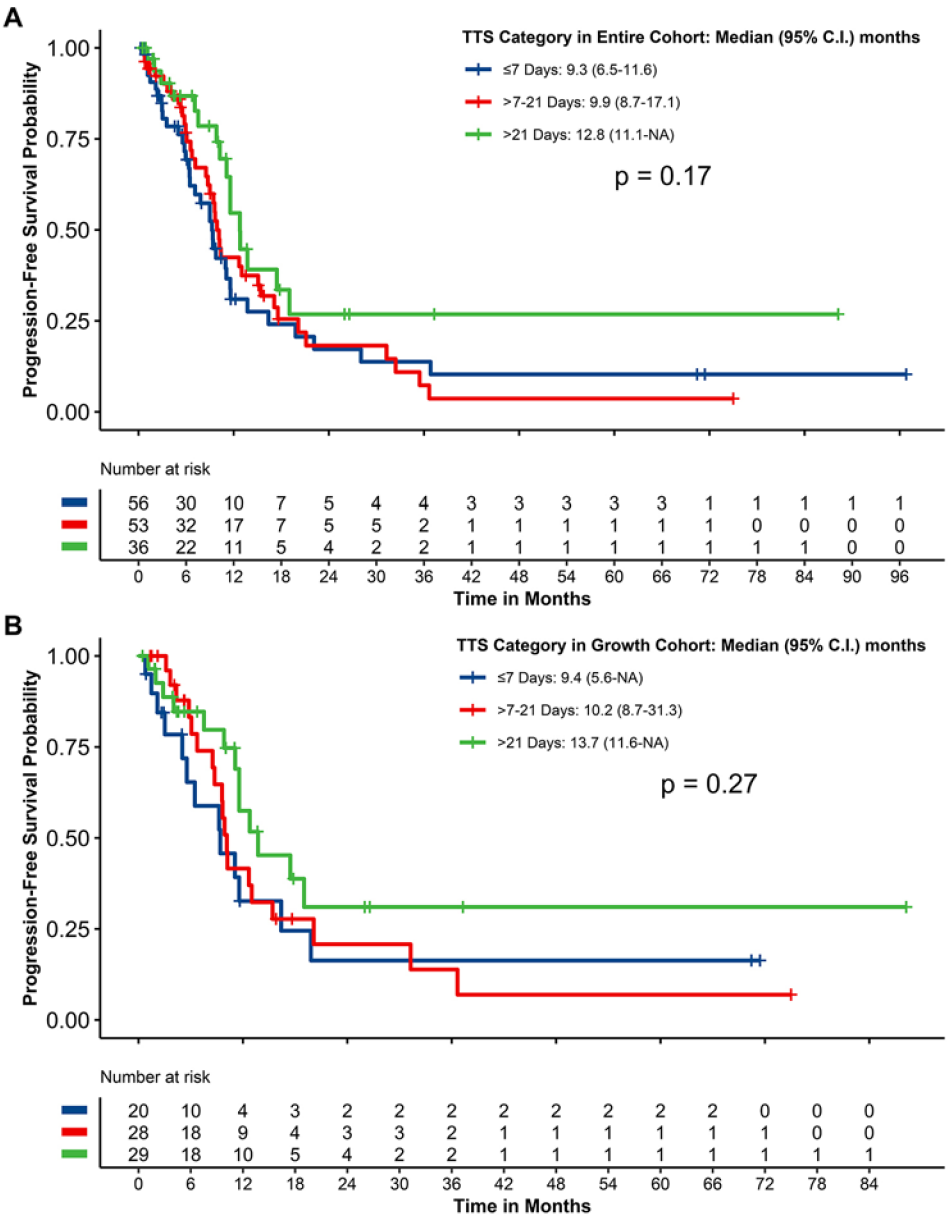

FIG. 5.

PFS by TTS category in the entire cohort (**A**) and growth cohort (**B**). Figure is available in color online only.

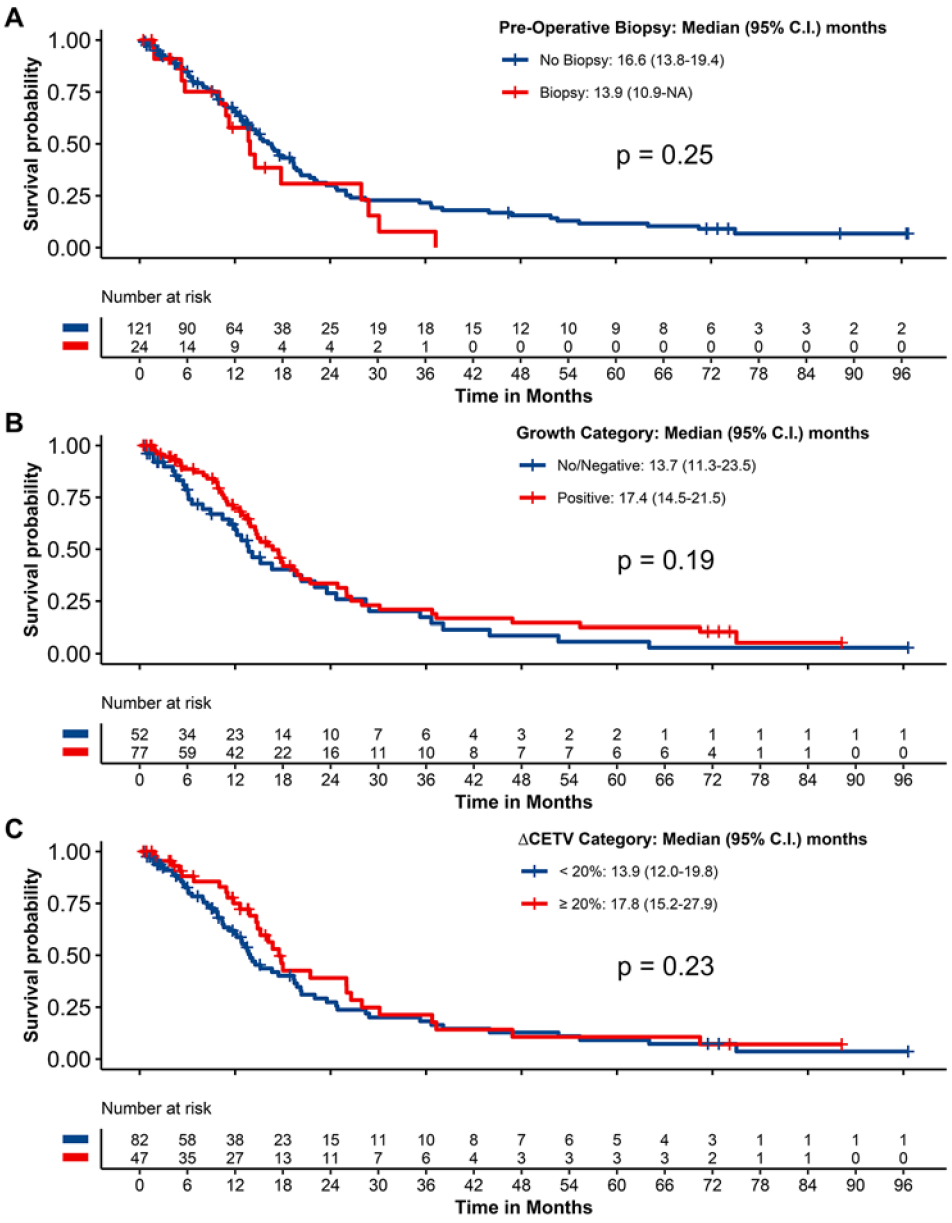

FIG. 6.

OS in the entire cohort by selected subgroups: preoperative biopsy (**A**), positive or no/negative growth (**B**), and growth ≥ or < 20% (**C**). Figure is available in color online only.

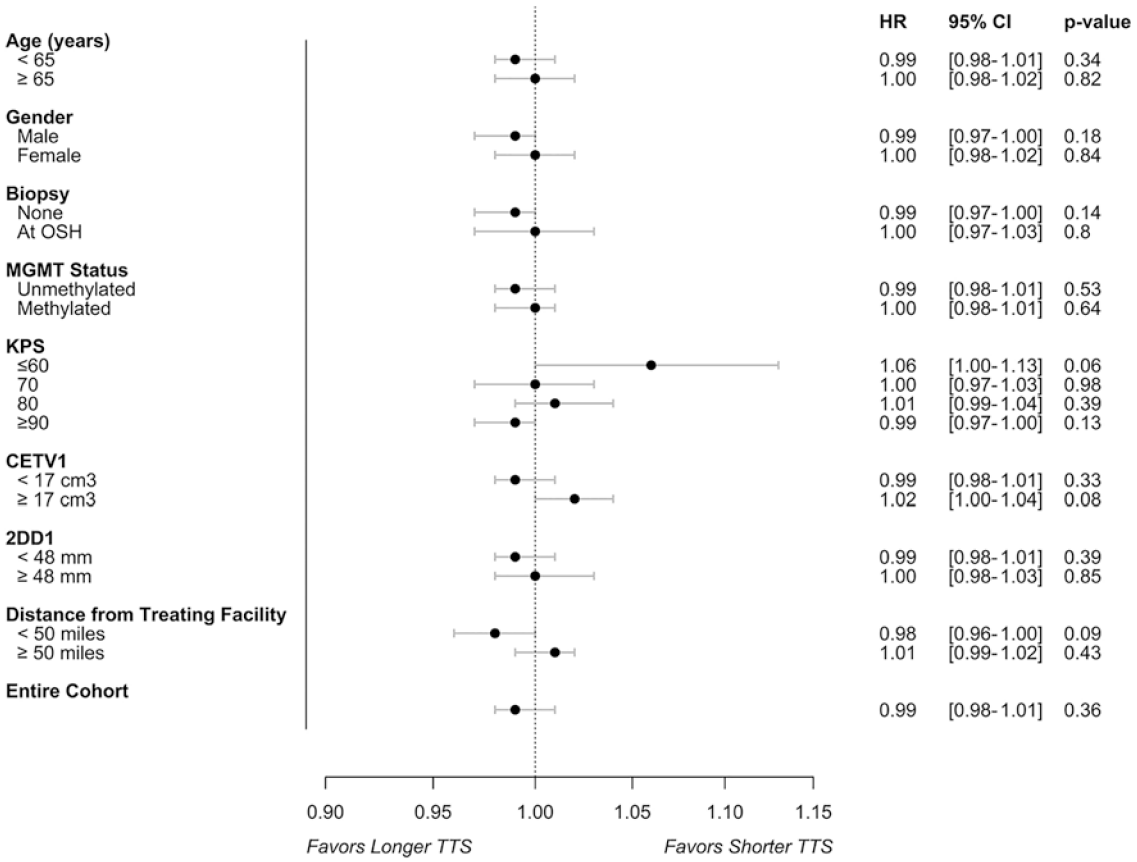

FIG. 7.

Cox regression analyses evaluating the effect of TTS on survival in selected subgroups.

TABLE 1.

Baseline demographic and clinical characteristics in the entire cohort by TTS category

Characteristic	Overall	TTS in Days			p Value
		≤7	>7–21	>21	
No. of patients	145	56 (39)	53 (37)	36 (25)	
Females	58 (40)	20 (36)	22 (42)	16 (44)	0.7
Age in yrs	62.39 (31.46–82.60)	60.25 (31.46–80.59)	62.04 (38.33–82.60)	64.23 (33.78–82.10)	0.094
Insurance					
Medicare	59 (41)	16 (29)	24 (45)	19 (53)	**0.043**
Private	59 (41)	23 (41)	21 (40)	15 (42)	>0.9
Medicaid	13 (9)	10 (18)	2 (4)	1 (3)	**0.021**
Uninsured/unknown	13 (9)	6 (11)	6 (11)	1 (3)	0.3
Other government	1 (1)	1 (2)	0 (0)	0 (0)	>0.9
Biopsy at OSH	24 (17)	0 (0)	11 (21)	13 (36)	**<0.001**
TTS in days	10.00 (1.00–82.00)	4.00 (1.00–7.00)	11.00 (8.00–21.00)	30.00 (22.00–82.00)	**<0.001**
Time to preop MRI in days	9.00 (0.00–81.00)	1.50 (0.00–6.00)	10.00 (2.00–20.00)	28.50 (21.00–81.00)	**<0.001**
New multifocal lesion	6 (4)	1 (2)	2 (4)	3 (8)	0.3
Transfer/delay initiator					0.4
Physician	104 (74)	42 (81)	37 (70)	25 (69)	
Patient	37 (26)	10 (19)	16 (30)	11 (31)	
Transfer/delay reason					**<0.001**
Higher level of care	54 (38)	30 (58)	19 (36)	5 (14)	
Referral	31 (22)	4 (8)	13 (25)	14 (39)	
Second opinion	31 (22)	8 (15)	13 (25)	10 (28)	
Mapping	22 (16)	9 (17)	7 (13)	6 (17)	
Other	3 (2)	1 (2)	1 (2)	1 (3)	
Distance from treating hospital in miles	57.19 (0.00–2575.49)	51.99 (0.00–2575.49)	59.58 (1.29–929.57)	57.19 (0.00–2575.49)	0.2
Distance from treating hospital >50 miles	53 (37)	18 (32)	19 (36)	16 (44)	0.5
Inside HSA	10 (7)	5 (9)	4 (8)	1 (3)	0.7
Presentation to OSH					**<0.001**

Characteristic	Overall	TTS in Days			p Value
		≤7	>7–21	>21	
ED	91 (65)	46 (88)	35 (66)	10 (28)	
Clinic	50 (35)	6 (12)	18 (34)	26 (72)	
Presentation to treating hospital					**<0.001**
Clinic	81 (56)	6 (11)	39 (74)	36 (100)	
Direct admit	51 (35)	37 (66)	14 (26)	0 (0)	
ED	13 (9)	13 (23)	0 (0)	0 (0)	
Tumor laterality					**0.031**
Lt	82 (57)	25 (45)	31 (58)	26 (72)	
Rt	62 (43)	31 (55)	21 (40)	10 (28)	
Bilat	1 (1)	0 (0)	1 (2)	0 (0)	
Tumor location					0.5
Frontal	47 (32)	22 (39)	13 (25)	12 (33)	
Temporal	47 (32)	16 (29)	20 (38)	11 (31)	
Parietal	34 (23)	11 (20)	14 (26)	9 (25)	
Insula	6 (4)	3 (5)	2 (4)	1 (3)	
Cingulate	4 (3)	1 (2)	3 (6)	0 (0)	
Occipital	4 (3)	1 (2)	0 (0)	3 (8)	
Thalamus	3 (2)	2 (4)	1 (2)	0 (0)	
Preop KPS	80.00 (20.00–100.00)	80.00 (20.00–100.00)	80.00 (50.00–100.00)	80.00 (50.00–100.00)	0.073
Preop deficits					
Seizures	48 (33)	15 (27)	15 (28)	18 (50)	0.06
Motor deficit	49 (34)	22 (39)	14 (26)	13 (36)	0.3
Behavioral changes	14 (10)	11 (20)	3 (6)	0 (0)	**0.005**
Confusion	48 (33)	23 (41)	13 (25)	12 (33)	0.2
Language deficit	69 (48)	23 (41)	28 (53)	18 (50)	0.5
Headache	64 (44)	25 (45)	24 (45)	15 (42)	>0.9
Nausea/vomiting	19 (13)	10 (18)	8 (15)	1 (3)	0.085
CN deficit	10 (7)	6 (11)	2 (4)	2 (6)	0.4

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Characteristic	Overall	TTS in Days			p Value
		≤7	>7–21	>21	
Visual deficit	34 (23)	12 (21)	11 (21)	11 (31)	0.5
Sensory deficit	24 (17)	8 (14)	8 (15)	8 (22)	0.6
Gait imbalance	34 (2)	15 (27)	12 (23)	7 (19)	0.7
Incidental	2 (1)	0 (0)	2 (4)	0 (0)	0.2
Postop KPS	80.00 (20.00–100.00)	80.00 (20.00–100.00)	80.00 (50.00–100.00)	80.00 (20.00–100.00)	0.7
Postop deficits					
New motor	13 (9)	7 (13)	3 (6)	3 (8)	0.5
New language	10 (7)	2 (4)	4 (8)	4 (11)	0.3
Preop deficit status					0.7
Improved	81 (57)	33 (60)	31 (61)	17 (47)	
Stable	35 (25)	13 (24)	11 (22)	11 (31)	
Worsened	26 (18)	9 (16)	9 (18)	8 (22)	
Postop deficit status					>0.9
No postop deficit	111 (77)	42 (75)	41 (77)	28 (78)	
Stable	16 (11)	7 (13)	5 (9)	4 (11)	
Improved	12 (8)	5 (9)	5 (9)	2 (6)	
Back to baseline	4 (3)	1 (2)	2 (4)	1 (3)	
Worsened	2 (1)	1 (2)	0 (0)	1 (3)	
Early complication	14 (10)	7 (13)	2 (4)	5 (14)	0.2
Late complication	4 (3)	0 (0)	1 (2)	3 (8)	0.066
Length of stay in days	4.00 (2.00–27.00)	6.00 (2.00–12.00)	3.00 (2.00–18.00)	3.00 (2.00–27.00)	**<0.001**
Discharge location					0.14
Home	98 (68)	35 (63)	40 (75)	23 (64)	
Acute rehab	36 (25)	15 (27)	13 (25)	8 (22)	
Home w/ services	9 (6)	5 (9)	0 (0)	4 (11)	
Deceased	2 (1)	1 (2)	0 (0)	1 (3)	
Postop radiation	113 (93)*	47 (98)*	41 (91)*	25 (89)*	0.2
Postop chemo	107 (88)*	42 (88)*	41 (89)*	24 (86)*	>0.9

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Characteristic	Overall	TTS in Days			p Value
		≤7	>7–21	>21	
PTEN deletion	100 (70) *	38 (70) *	35 (66)	27 (75)	0.7
EGFR amplification	59 (41)	28 (50)	18 (34)	13 (36)	0.2
MGMT methylation	70 (48)	28 (50)	23 (43)	19 (53)	0.7
ATRX retained	138 (95)	51 (91)	52 (98)	35 (97)	0.2
Progression	89 (61)	36 (64)	37 (70)	16 (44)	**0.044**
Mortality	102 (70)	41 (73)	36 (68)	25 (69)	**0.8**
EOR	98.07 (28.68–100.00)	98.15 (35.80–100.00)	98.43 (28.68–100.00)	97.79 (50.00–100.00)	0.8
Volumetric increase from initial MRI	77 (53)	20 (36)	28 (53)	29 (81)	**<0.001**

chemo = chemotherapy; CN = cranial nerve; rehab = rehabilitation.

Values are expressed as number (%) for categorical data or as median (minimum–maximum) for continuous data. Boldface type indicates statistical significance.

* Data missing for some cases.